

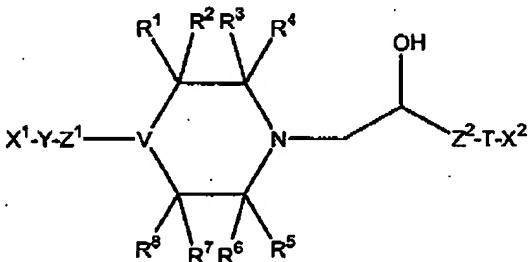
Response to July 6, 2005, Office Action
 Atty Dkt No. 03-0185
 Application No. 10/759,555

APPENDIX A

CLEAN COPY OF CLAIMS AS AMENDED HEREIN

1. A compound of Formula I:

wherein:



Formula I

R¹, R², R³, R⁴, R⁵, R⁶, R⁷, and R⁸ are hydrogen, lower alkyl, or -C(O)R;

in which R is -OR⁹ or -NR⁹R¹⁰, where R⁹ and R¹⁰ are hydrogen or lower alkyl; or R¹ and R², R³ and R⁴, R⁵ and R⁶, R⁷ and R⁸, when taken together with the carbon to which they are attached, represent carbonyl; or

R¹ and R⁵, or R¹ and R⁷, or R³ and R⁵, or R³ and R⁷, when taken together form a bridging group -(CR¹²R¹³)_n-, in which n is 1, 2 or 3, and R¹² and R¹³ are independently hydrogen or lower alkyl;

with the proviso that

- (a) the maximum number of carbonyl groups is 1;
- (b) the maximum number of -C(O)NR⁹R¹⁰ groups is 1; and
- (c) the maximum number of bridging groups is 1;

T is oxygen, sulfur, or NR¹¹, in which R¹¹ is hydrogen or lower alkyl;

V is -N<;

X¹ is hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

X² is optionally substituted aryl or optionally substituted heteroaryl;

Y is optionally substituted dihydroheteroaryl; and

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Z^1 and Z^2 are independently optionally substituted alkylene of 1-4 carbon atoms.

2. A compound of claim 1, wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^8 are independently chosen from hydrogen and methyl

3. A compound of claim 2, wherein X^1 is optionally substituted aryl and X^2 is optionally substituted heteroaryl.

4. The compound of claim 3, wherein Z^1 is methylene and Z^2 is methylene or ethylene.

5. The compound of claim 4, wherein Y is optionally substituted dihydroheteroaryl in which the hetero atoms are chosen from nitrogen and oxygen.

6. The compound of claim 5, wherein T is oxygen, X^1 is optionally substituted phenyl, and Y is optionally substituted isoxazolyl.

7. The compound of claim 6, wherein X^2 is optionally substituted benzothiazolyl.

8. The compound of claim 7, wherein Y is optionally substituted 5-(4,5-dihydroisoxazol-3-yl).

9. The compound of claim 8, wherein X^1 is 4-(trifluoromethyl)phenyl, X^2 is 2-methylbenzothiazol-5-yl, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^8 are hydrogen, and Z^2 is methylene, namely 1-(2-methylbenzothiazol-5-yloxy)-3-[4-(5-[4-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)methyl)piperazinyl]propan-2-ol.

10. The compound of claim 9, namely (2R)-1-(2-methylbenzothiazol-5-yloxy)-3-[4-(5-[4-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)methyl)piperazinyl]propan-2-ol.

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11. The compound of claim 8, wherein X^1 is 2-(trifluoromethyl)phenyl, X^2 is 2-methylbenzothiazol-5-yl, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^8 are hydrogen, and Z^2 is methylene, namely 3-(2-methylbenzothiazol-5-yloxy)-1-[4-(5-[2-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]propan-2-ol.

12. The compound of claim 11, namely (2R)-3-(2-methylbenzothiazol-5-yloxy)-1-[4-(5-[2-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]propan-2-ol.

13. The compound of claim 8, wherein X^1 is 4-(trifluoromethyl)phenyl, X^2 is 2-methylbenzothiazol-5-yl, R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , and R^8 are hydrogen, R^3 is (S)-methyl, and Z^2 is methylene, namely 1-[(2S)-2-methyl-4-(5-[4-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

14. The compound of claim 13, namely (2R)-1-[(2S)-2-methyl-4-(5-[4-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

15. The compound of claim 8, wherein X^1 is 2-(trifluoromethyl)phenyl, X^2 is 2-methylbenzothiazol-5-yl, R^1 , R^3 , R^2 , R^4 , R^5 , R^6 , and R^8 are hydrogen, R^7 is (S)-methyl, and Z^2 is methylene, namely 1-[(3S)-3-methyl-4-(5-[2-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

16. The compound of claim 15, namely (2R)-1-[(3S)-3-methyl-4-(5-[2-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

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17. The compound of claim 8, wherein X^1 is 4-(trifluoromethyl)phenyl, X^2 is 2-methylbenzothiazol-5-yl, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^8 are hydrogen, R^7 is (S)-methyl, and Z^2 is methylene, namely 3-[(3S)-3-methyl-4-({5-[4-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

18. The compound of claim 17, namely (2R)-3-[(3S)-3-methyl-4-({5-[4-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

19. The compound of claim 8, wherein X^1 is 2-(trifluoromethyl)phenyl, X^2 is 2-methylbenzothiazol-5-yl, R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , and R^8 are hydrogen, R^3 is (S)-methyl, and Z^2 is methylene, namely 1-[(2S)-2-methyl-4-({5-[2-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

20. The compound of claim 19, namely (2R)-1-[(2S)-2-methyl-4-({5-[2-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

21. The compound of claim 7, wherein Y is optionally substituted 3-(4,5-dihydroisoxazol-5-yl).

22. The compound of claim 21, wherein X^1 is 4-(trifluoromethyl)phenyl, X^2 is 2-methylbenzothiazol-5-yl, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^8 are hydrogen, and Z^2 is methylene, namely 1-[4-({3-[4-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-5-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

23. The compound of claim 22, namely (2R)-1-[4-({5R)-3-[4-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-5-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

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24. The compound of claim 21, wherein X¹ is 2-(trifluoromethyl)phenyl, X² is 2-methylbenzothiazol-5-yl, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, and R⁸ are hydrogen, and Z² is methylene, namely 1-[4-(3-[2-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-5-yl)methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

25. The compound of claim 24, namely (2R)-1-[4-((5R)-3-[2-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-5-yl)methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

26. The compound of claim 21, wherein X¹ is 4-fluorophenyl, X² is 2-methylbenzothiazol-5-yl, R¹, R², R⁴, R⁵, R⁶, R⁷, and R⁸ are hydrogen, R³ is (S)-methyl, and Z² is methylene, namely 1-(4-((5R)-3-(4-fluorophenyl)(4,5-dihydroisoxazol-5-yl)methyl)(2S)-3-methylpiperazinyl)-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

27. The compound of claim 26, namely (2R)-1-(4-((5R)-3-(4-fluorophenyl)(4,5-dihydroisoxazol-5-yl)methyl)(2S)-3-methylpiperazinyl)-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

28. The compound of claim 21, wherein X¹ is phenyl, X² is 2-methylbenzothiazol-5-yl, R¹, R², R⁴, R⁵, R⁶, R⁷, and R⁸ are hydrogen, R³ is (S)-methyl, and Z² is methylene, namely 1-(4-((5R)-3-phenyl(4,5-dihydroisoxazol-5-yl)methyl)(2S)-2-methylpiperazinyl)-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

29. The compound of claim 28, namely (2R)-1-(4-((5R)-3-phenyl(4,5-dihydroisoxazol-5-yl)methyl)(2S)-2-methylpiperazinyl)-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

30. A method of treating a disease state chosen from diabetes, damage to skeletal muscles resulting from trauma or shock and a cardiovascular disease in a mammal by administration of a therapeutically effective dose of a compound of claim 1.

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31. The method of claim 30, wherein the cardiovascular disease is atrial arrhythmia, intermittent claudication, ventricular arrhythmia, Prinzmetal's (variant) angina, stable angina, unstable angina, congestive heart disease, or myocardial infarction.
32. The method of claim 30, wherein the disease state is diabetes.
33. A pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and a therapeutically effective amount of a compound of claim 1.